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ORIGINAL ARTICLE.

Impact of Albumin to Globulin Ratio on The Outcome of Women with Metastatic Breast Cancer

Shereen Elshorbagy[1], Rana Ebied[2*], Ola Elfarargy[1]
[1]Medical Oncology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[2]Medical oncology Department, Al Ahrar Teaching Hospital, Zagazig, Egypt

Corresponding author*
Rana Ahmed Ebied

E-mail:
ranaebeed.2019@gmail.com
Medical Oncology Department Al Ahrar Teaching Hospital, Zagazig, Egypt

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ABSTRACT:

BACKGROUND: Breast cancer is the most frequent malignancy among women all over the globe. The albumin/globulin ratio (AGR) is a simple and cost-effective inflammatory measure that is strongly related with cancer patient prognosis and treatment response. Aim: To evaluate the prognostic impact of albumin to globulin ratio on the outcome of women with metastatic breast cancer.

METHODS: This study is a retrospective analysis of data obtained from sixty female patients diagnosed with metastatic breast cancer and treated in Medical Oncology Department, Zagazig University from January 2015 to December 2017. Several variables were extracted anonymously from patients' medical records, then were analyzed by applying receiver operating curve (ROC) analysis.

RESULTS: Kaplan Meier survival curves disclosed a 5-year overall survival rate which differed significantly in patients as regard the AGR ($p < 0.001$), with AGR cut-off value (≤1.1). The 5-year overall survival rate was 35%. On the other side, there were no statistically significant differences between neither AGR and PFS ($p = 0.297$), nor clinical or pathologic criteria of our studied patients. **CONCLUSIONS:** Statistically significant correlation was found between AGR and OS; high AGR was associated with prolonged OS. Nevertheless, according to follow-up, a long-term follow-up should be done to assess its prognostic significance for disease-free survival.

KEYWORDS: Breast Cancer; Metastatic; Albumin Globulin Ratio

INTRODUCTION

Breast cancer is the most frequent malignancy among women all over the world, and although; it is the second cause of mortality among women from cancer its prevention remains a challenge across the world [1]. Patients with metastatic breast cancer (MBC) who were classified as Stage IV can achieve complete clinical response and survive for a long time after multidisciplinary treatment. In this case, the 10-year survival rate of MBC can reach 15.6% while the 5-years survival rate can reach 32.6% [2]

Cancer related inflammation plays a key role in the onset and progression of cancer; and may plays a role in the therapy outcome. In patients with cancer, the systemic inflammatory reaction has been found to be an independent predictive factor. The albumin to globulin ratio (AGR) is a simple and cost-effective inflammatory measure that correlates with patient prognosis and treatment response [3]. The nutritional status of cancer patients is routinely assessed using serum albumin that also is linked to the host's systemic inflammatory response. There are various members of the globulin family, for example, alpha, beta, and gamma globulins. Globulins are produced by B cells of the adaptive immune system, and are known as immunoglobulins or antibodies. As a result, they play a crucial role in immunity, and the amount of globulin in the blood has been linked to chronic inflammation [4].

AIM: To assess if the albumin to globulin ratio has any prognostic value on the disease's outcome in women with metastatic breast cancer.

METHODS

Study design: After approval by the Research Ethical Committee of Faculty of Medicine, Zagazig University (Institutional Research Board

"IRB"), the work has been carried out in accordance to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans, who were assessed in the sample size, procedures, and scientific background. This study retrospectively included sixty women aged ≥ 18 year, with available full data, and diagnosed with metastatic breast cancer, either de novo or were treated according to their primary physician plan with hormonal therapy, chemotherapy, or targeted therapy in Medical Oncology Department, Zagazig University from January 2015 to December 2017 were included. Patients had malignancy other than BC, and/or cases with incomplete data were excluded from the study. Data including personal data, medical history, surveillance/follow-up data after the end of the adjuvant therapy, and pathological data. Last one involved the following: the extent, metastasis, tumor estrogen / progesterone receptor (ER/PR), HER2 status, and Ki67 assessment was namelessly extracted from patients' medical records, then was transcribed into an Excel spreadsheet. Also; Albumin to Globulin Ratio was calculated as serum albumin / (total protein-albumin); the values were documented at time of metastasis and before starting any treatment by applying receiver operating curve (ROC) analysis. Association between Albumin globulin ratio and clinical-pathological data of metastatic breast cancer was analyzed. In addition, associations between Albumin to Globulin Ratio and progression free survival (PFS) that; defined as the time between date of first treatment and date of disease progression, and the overall survival (OS) the interval from diagnosis to death or last follow up visit in cases with metastatic breast cancer.

Statistical Analysis:

A receiver operating characteristic (ROC) curve was constructed to permit selection of the cut-off point of AGR for survival outcome (dead/alive) of metastatic breast cancer patients. Data were tested for normal distribution using the Shapiro-Walk test. Categorical covariates were compared using the Chi-square test or Fisher's exact test. Mann-Whitney U Test was used to calculate difference between quantitative variables in more than two groups along with Dunn's Post hoc test for multiple comparisons. Spearman's correlation test was used for correlating non-parametric variables. The OS and PFS were calculated by the Kaplan-Meier method, and survival curves were compared using the Log-rank test. All tests were two-sided; a p value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS 24 Inc. Chicago, IL, USA).

RESULTS

Our patients' ages ranged from 23-to-70 years, about thirteen percent (13.3%) of patients had positive family history of breast cancer, majority (45/60,75%) of them had invasive ductal carcinoma (IDC) while the remaining (15/60, 25%) had invasive lobular carcinoma(ILC), about 61.7% of the patients were postmenopausal, the majority of patients (29/60, 48.3%) had histological grade II tumors, Ki-67 was high with cut-off value > 20% in 25 patients (25/60, 41.66%), eighteen patients (18/60, 30%) showed positive HER2-neu status, about sixty sex percent (40/60, 66.7%) showed ER positive, and thirty three patient (33/60, 55%) were positive progesterone receptor (PR). Half of studied patients (30/60, 50%) were luminal A. On the other hand; luminal B represented 31.67%, triple negative comprised 6.67% of them while HER-2neu enriched were 11.67%. Multiple metastasis rather than single in 65%. Albumin was ranged from 1.7-5 gm/dl, with a median 3.65 gm/dl. While; globulin was ranged from 2-5.6 gm/dl, with a median 3gm/dl. The median value of AGR was 1.15 (Table 1). As regard therapy before diagnosis of metastatic breast cancer, forty patients (40/60, 66.6%) were on hormonal therapy, eighteen patients (18/60, 30%) were on targeted therapy, and forty-one (41/60, 68.3%) were treated with chemotherapy, while; seventeen patients (17/60, 28.3%) were newly diagnosed (Table 2). AGR value < 1.1 showed AUC of 0.853 (95% CI, 0.738-0.931) with a sensitivity of 74.36% (95% CI, 57.9- 87.0%), and a specificity of 95.24% (95% CI, 76.2 - 99.9%) for diagnosis of survival (Table 3). Based on the initial AGR level; the sixty cases with metastatic breast cancer were classified into 2 groups: low and high, and showed no statistically significant correlation to clinical-pathological variables including; age, body surface area (Table 4, 5). The 5-year overall survival was significantly higher in patient with high AGR (p-value <0.001). However; progression free survival, after a median follow-up period for 3 years, and yielded (1-5) years showed no significant (p-value 0.315) difference between the two groups (Table 6 ,7).

Table (1): Baseline patient characteristics

Variable					Total n.= 60	
		Median		Range	n.	%
Age (years)		52.5		(23-70)		
Surface area of the body (m2)		1.7		(1.5-2)		
Menopausal state	**No**				23	38.33%
	Yes				37	61.67%
Family history	**Yes**				8	13.33%
	No				52	86.67%
Histopathology	**Invasive ductal carcinoma**				45	75.00%
	Invasive lobular carcinoma				15	25.00%
Grade	**G1**				6	10.00%
	G2				29	48.33%
	G3				25	41.66%
Estrogen receptor	**Positive**				40	66.67%
	Negative				20	33.33%
Progesterone receptor	**Positive**				33	55.00%
	Negative				27	45.00%
HER2neu	**Positive**				18	30.00%
	Negative				42	70.00%
KI67	**High**				25	41.66%
	Low				35	58.44 %
Molecular subtypes	**Luminal A**				30	50.00%
	Luminal B				19	31.67%
	Her2 Enriched				7	11.67%
	Triple -Ve				4	6.67%
Number of metastasis	**one**				21	35.00%
	More than one				39	65.00%
Follow-up period (years)		3	1-5			
Albumin (gm/dl)		3.65	1.7-5			
Globulin (gm/dl)		3	2-5.6			
Albumin/Globulin ratio		1.15	0.5-1.9			

Continuous data are presented as median (range) or number& (%)

Table (2): Type of therapy before diagnosis of metastatic breast cancer

Type of therapy	Total number = 60	
	Number	%
Chemotherapy	41	68.3%
Target therapy	18	30%
Hormonal therapy	40	66.6%
No previous therapy (De novo cases)	17	28.3%

De novo cases; initially diagnosed with metastatic breast cancer.

Table (3): Receiver operating characteristic curve (ROC) and area under the curve (AUC) for AGR at diagnosis for survival analysis

Cut-off	Sensitivity % 95% CI	Specificity % 95% CI	PPV % 95% CI	NPV % 95% CI	AUC 95% CI	P
AGR < 1.1	74.36 57.9 - 87.0	95.24 76.2 - 99.9	96.7 80.9 - 99.5	66.7 53.7 - 77.5	0.853 0.738 - 0.931	<0.001

AGR: Albumin/Globulin Ratio

Table (4): Baseline patient characteristics [median (range) or n. (%)] based on the AGR Level

		AGR Level				P
		Low N=30		High N=30		
		N	%	N	%	
Age (years)*		54 (23-70)		50 (25-70)		0.451
Surface area of the body (m^2)		1.7 (1.5-2)		1.6 (1.5-2)		0.144
Menopausal state	**Pre**	9	30.00%	14	46.67%	0.184
	Post	21	70.00%	16	53.33%	
Family history	**Yes**	3	10.00%	5	16.67%	0.754
	No	27	90.00%	25	83.33%	
Histopathology	**IDC**	22	73.33%	23	76.67%	0.766
	ILC	8	26.67%	7	23.33%	
Grade	**G1**	4	13.33%	2	6.67%	0.51
	G2	12	41.37%	17	58.62%	
	G3	11	44.00%	14	56.00%	
Estrogen receptor	**Positive**	20	66.67%	20	66.67%	1
	Negative	10	33.33%	10	33.33%	
Progesterone receptor	**Positive**	16	53.33%	17	56.67%	0.795
	Negative	14	46.67%	13	43.33%	
HER2neu	**Positive**	6	20.00%	12	40.00%	0.37
	Negative	24	80.00%	18	60.00%	
KI67	**High**	12	48.00%	13	52.00%	0.121
	Low	18	51.42%	17	48.57%	
Molecular type	**Luminal A**	11	36.67%	8	26.67%	0.619
	Luminal B	3	10.00%	4	13.33%	
	Her2 Enriched	13	43.33%	17	56.67%	
	Triple -Ve	3	10.00%	1	3.33%	
Number of metastasis	**Single**	8	26.67%	13	43.33%	0.176
	Multiple	22	73.33%	17	56.67%	
Albumin/globulin ratio		0.8 (0.5-1.1)		1.4 (1.2-1.9)		<0.001
Albumin (gm/dl)*		2.9 (1.7-4.7)		4.2 (3.3-5)		<0.001
Globulin (gm/dl)*		3.2 (2.2-5.6)		3 (2-3.4)		0.001

All variables were compared using Chi-square X2 test except (*) Mann Whitney test

Table (5): correlation between the Albumin/Globulin ratio(AGR) at diagnosis and other studied parameters

Parameters	AGR	
	r	P
Age (years)	-0.137	0.295
Surface area of the body (m^2)	-0.195	0.135

r = Correlation Coefficient, P ≤ 0.05 means significant

Table (6): The 5-year overall survival (OS) rate in relation to Albumin/Globulin ratio

OS		Total n.	N of Events	Censored		Overall Survival	p	Survival Time (years)			
				n.	Percent	Rate%		mean ±SE	95% CI	median ±SE	95% CI
AGR level	High	30	10	20	66.70%	66.70%	<0.001	4.2 ±0.21	3.78-4.61	NR	
	Low	30	29	1	3.30%	3.30%		2.87 ±0.19	2.5-3.23	3 ±0.19	2.63-3.37
Overall		60	39	21	35.00%	35.00%		3.53 ±0.17	3.21-3.86	3 ±0.3	2.42-3.58

SE: std. error, 95% Confidence Interval. Continuous data are presented as number and percentage

Table (7): The 5-year progression free survival(PFS) rate according to Albumin/Globulin ratio (AGR)

PFS	Total n.	n. of Events	Censored		Survival Rate%	p	Survival period (years)			
			n.	%			Mean ±SE	95% CI	median ±SE	95 % CI
AGR Level	Low	30 15	15	50%	50%	0.315	2.78 ±0.41	1.98-3.57	0.80	
	High	30 11	19	63.3 %	63.30%		3.37 ±0.39	2.6-4.14	NR	
Overall	60	26	34	56.7 %	56.7%		3.07 ±0.28	2.51-3.63	NR	

SE: std. error, 95% Confidence Interval, NR: not reached. continuous data are presented as number and percentage.

Table (8): Univariate and multivariate Cox regression analyses for overall survival

Variable	Univariate				Multivariate			
	Sig.	HR	95.0% CI for HR		Sig.	HR	95.0% CI for HR	
			Lower	Upper			Lower	Upper
Age (years)	0.094	1.02	1.00	1.05	0.525	0.98	0.93	1.04
Menopausal state	0.015	2.44	1.19	5.04	0.312	2.22	0.47	10.47
Surface area of the body (m^2)	0.175	2.99	0.61	14.61				
Family history	0.047	2.59	1.01	6.65	0.085	3.54	0.84	14.93
Histopathology	0.463	1.32	0.63	2.78				
Grade 1	0.067	2.140.85 5.76			0.54	0.630.19 1.57		
Grade 2	0.079	2.31	0.91	5.88	0.195	0.49	0.17	1.44
Grade 3	0.857	1.07	0.53	2.13	0.55	0.74	0.27	2.00

Variable	Univariate				Multivariate			
	Sig.	HR	95.0% CI for HR		Sig.	HR	95.0% CI for HR	
			Lower	Upper			Lower	Upper
Estrogen receptor	0.352	1.36	0.71	2.59				
Progesterone receptor	0.206	1.50	0.80	2.82				
HER2neu	0.645	1.17	0.60	2.28				
KI67	0.122	0.60	0.32	1.14				
Molecular type Luminal A	0.653	1.32	0.32	4.76	0.732	0.74	0.13	3.18
Molecular type Luminal B	0.658	1.26	0.46	3.43	0.82	1.16	0.32	4.16
Molecular type Triple negative	0.688	1.31	0.35	4.88	0.722	0.76	0.17	3.48
Molecular type Her2 Enriched	0.071	2.57	0.92	7.16	0.066	3.43	0.92	12.74
Number of metastasis	0.238	1.23	0.87	1.75				
Progression	0.256	1.21	0.87	1.67				
AGR Low vs high	<0.001	0.21	0.10	0.45	0.014	3.61	1.29	10.08

DISCUSSION

The interaction between cancer cells and the host immune system is gaining more attraction with time. Breast cancer has a distinct and complex microenvironment that is rich in growth factors, proteinases, and inflammatory cytokines that help breast cancer cells proliferation, invasion, and spread [4]. In various types of malignancies e.g. hepatocellular carcinoma, small-cell lung cancer, and nasopharyngeal carcinoma the two key components of the systemic inflammatory response are albumin (ALB) and globulin (GLB) [5]. Combination of (AGR) and (GLB); had been shown to be important and negatively correlated with programmed death-1(PD-1) mRNA levels, suggesting that nutritional status has an impact on immunity in breast cancer patients [6]. The current study was a retrospective study evaluated the prognostic impact of albumin to globulin ratio on the outcome of 60 metastatic breast cancer women either de novo or post early presentation treatment; recorded data were obtained in Medical Oncology Department, Zagazig University Hospitals from records that documented the period between January 2015 and December 2017. The average follow-up duration was 3years, and ranged from1-5 years. Our patients were divided according to AGR cut-off value 1.15 determined by used receiver operating characteristic (ROC) curve analysis into two groups; AGR; < 1.15, and AGR ≥ 1.15. The median value of albumin was 3.65 gm/dl, and ranged from 1.7-5, the median value of globulin was 3mg/dl, and ranged from 2-5.6 gm/dl; this was near to Liu and colleagues' AGR cut-off value, who determined it using X-tile software to be 1.12. Then, the patients were divided into two groups; AGR < 1.12, and AGR ≥ 1.12 [6]. On the other hand, Xuan and colleagues found that the median value of albumin was 4.5 gm/dl, and ranged from 2.7–5.7), and the median value of globulin was 2.8 gm/dl (range: 1.6–4.5) with AGR cut-off value 1.63 [4]. Patients median age was 52.5 years, and ranged from 23-70 years that was similar to Liu and colleagues' patients; they reported a median age of 51, and ranged from 22–75) years with different breast cancer stages(I–IV) [7]. While Rubio and colleagues reported a median age of their patients 59 years, which may be explained by large number of patients with different included demographic features [8]. We found 13.3% of patients had positive family history, similarly; Murat and colleagues showed near result; 11.4% had positive family history and 63 patients had single bone metastasis developed ≥ 6 months after breast cancer diagnosis [9]. Adamowicz K, and colleagues' study showed that 53 patients had a positive family history 15% of 351 patients with advanced metastatic Breast Cancer [6]. Most of patients (75%) had invasive ductal carcinoma that was similar to Zewenghiel and colleagues'; invasive ductal carcinoma cases represented 76% of their patients [10]. Also; this was near to Petekkaya and colleagues, result that was 71.6% (60/83) of their included patients [11]. And in agreement with Simon, J and colleagues' results as regard the postmenopausal status; about 62% of their patients [12]. While; represented only 2.5% in a study done by Petekkaya and colleagues [11]. The majority of our included patients (48.3%) had histological grade II tumors. This result was similar to Petekkaya and colleagues; about 53% of their patients had grade II tumors [11]. In only 25 patients (42%) the Ki-

67 was high with a cut-off value of >20%. While high levels were seen in majority of cases (82%) in Shao, Y and colleagues' study, that can be explained by their low cut-off value of KI67(> 14%) [13]. As regard the hormonal status among studied groups, eighteen (30%) patients were HER2-neu positive, forty (66%) estrogen receptor (ER) positive, and progesterone receptor (PR) positive patients were thirty-three (55%). This was comparable to Matikas and colleagues' results; 22.5%, 52%, and 42.6% respectively [14]. Also; it was similar to Mills,J and colleagues' results; 28%, 64%,52% respectively[15]. As regard the molecular subtypes, half of patients were luminal A (30/60), 32% of patients were luminal B, only 6.67% showed triple negative and HER2-neu enriched was in 11.67%. These results were near to Lohmann and colleagues' results 87.5% of their patients showed hormone receptor–positive collectively,15.6% were HER2-neu enriched, and10.4% were triple-negative [16]. In the current study; metastasis was multiple rather than single in 65%; this was near to Rubio and colleagues who reported multiple visceral metastasis in 60% of their patients [8]. While; De Giorgi and colleagues reported three or more metastatic sites in 211 (40.8%) of their groups; 113 (53.6%) were visceral metastasis, 61.8% had < 5 circulating tumor cells (CTCs), while 98 (46.4%) had ⩾ 5 circulating tumor cells (p = 0.005) [17]. As regards therapy before diagnosis of metastatic breast cancer; forty-one patients (68.3%) were treated with chemotherapy, eighteen patients (30%) were on targeted therapy, forty patients (66.6%) were on hormonal therapy, with median time about nine months ranged from 3-30 months, and seventeen patients (28.3%) were newly diagnosed. This was comparable-to Lohmann and colleagues; fifty-three (55.2%) of their patients received chemotherapy, eight (8.3%) received targeted therapy, and thirty-three of them (34.4%) received hormonal therapy [16]. There was no statistically significant correlation between AGR and patients' clinical-pathological variables; this result was similar to Xuan and colleagues [4]. A median period of 3 years of follow-up (ranged from1-5 years) revealed that AGR cannot determine the PFS (p=0.297) but, in univariate analysis; significantly (p=< 0.001) predict the overall survival (OS). In a Systematic Review and Meta-analysis by He J and colleagues, a total of 13890 solid tumor patients in 24 studies were included; (354) of them were diagnosed with mixed stages breast cancer. An AGR with cut-off values ranging from 1.15 to 1.7 was associated with better OS (HR=0.58, 95%CI 0.537-0.626, p < 0.0001) [18]. Chi and colleagues showed that there was a significant increase in the risk of Lymph node metastasis (LNM) in group with low AGR when compared to group with high AGR (HR=2.24, 95% CI=1.49-3.36, P<0.001). AGR showed positive correlation with OS and LNM in patients with cancer, and so can be used as a marker in assessment of prognosis those patients. In a study by Xuan and colleagues; included 289 cases showed prolonged PFS with high AGR group (p = 0.025), and they concluded that the pre-treatment AGR was an independent and significant predictor of PFS in triple negative breast cancer patients [4]. Also; Yakup and colleagues found that low AGR was an independent bad risk factor in patients with metastatic gastric cancer both in terms of OS (p = 0.019, Hazard Ratio (HR) = 1.380, 95% Confidence Interval (CI) = 1.055-1.805) and PFS (p = 0.002, HR = 1.514, 95% CI = 1.164-1.968) [20]. And Lu and colleagues revealed that AGR was an independent prognostic factor in terms of OS and PFS in metastatic NSCLC [21].

Limitations: First; the cohort reported was small, second; as the study was retrospective, patient records were heavily relied upon.

CONCLUSIONS

Multivariate analysis including the significant parameters (p ≤ 0.05) in univariate analysis; revealed statistically significant correlations between AGR and overall survival. As breast cancer has wide heterogeneity; AGR cut-off value was limited to cases with metastatic breast cancer only. So; more researches including more groups of breast cancer, and evaluating more novel biomarkers is recommended to be employed in clinical practice, and be used as a significant prognostic indicator for disease-free survival in breast cancer

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